Global **Malaria** Programme

Determining non-inferiority of insecticide-treated nets and indoor residual spray products within an established product class

Evidence Review Group meeting report
5–6 July 2018 Geneva, Switzerland

World Health Organization

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This publication contains the report of the meeting of the Evidence review group on determining non-inferiority of insecticide-treated net and indoor residual spraying products within an established class and does not necessarily represent the decisions or policies of WHO.

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BACKGROUND

As of 1 January 2017, WHO started to implement a new process for evaluating vector control products so as to better meet the needs of countries endemic for or at risk of vector-borne diseases. The aim of the new process is to provide enhanced assurance regarding product safety, quality and efficacy. Guidance to ensure these enhancements is evolving.

One area that urgently requires additional evaluation and guidance on how to conduct such evaluation is ensuring that a policy recommendation based on epidemiological evidence demonstrating the public health value of a 'first-in-class' product can with reasonable certainty be applied to 'second-in-class' products, which are not required to demonstrate epidemiological impact. This case is exemplified by mosquito nets treated with a pyrethroid insecticide and the synergist piperonyl butoxide (PBO).

Pyrethroid-PBO nets were given an interim endorsement as a new product class in 2017 *(1)* based on epidemiological data demonstrating the efficacy of one product, generated through one cluster randomized trial conducted with Olyset®Plus (manufactured by Sumitomo Chemicals Co. Ltd) *(2)*. At the time, four other net products containing PBO had been assessed and recommended by the WHO Pesticide Evaluation Scheme (WHOPES) as pyrethroid nets. In the transition from WHOPES to the new WHO evaluation system, these recommendations were converted to a prequalification listing. However, the four nets differ from Olyset® Plus in terms of their design/specifications. Key differences include: the location of the PBO (i.e., all net panels or just the top panel); the PBO loading dose; the type and content of pyrethroid; and the regeneration time and wash resistance of the PBO. Therefore, it remains unclear whether these second-in-class products should be covered by the policy recommendation that was developed based on the epidemiological data generated by the first-in-class product (in this case Olyset®Plus). Guidance is needed to support generation of data to provide clarity in this area.

An Evidence Review Group (ERG) was held in September 2017 to determine the data requirements and methods to support the evaluation of new vector control products *(3)*. A discussion was initiated on the further assessment of pyrethroid-PBO nets and other key areas that require better evidence to inform WHO guidance to Member States. Following the presentation of the ERG deliberations to the Malaria Policy Advisory Committee (MPAC), one of the recommendations to WHO was that vector control products with the same biochemical mode of action[1] and entomological effect[2] as a product in a class covered by a WHO policy recommendation should be required to:

- Meet current testing criteria for the product class based on laboratory studies[3], small-scale field trials[4] and large-scale field trials[5] with entomological endpoints. Current guidance for each intervention type (insecticide-treated nets [ITNs], indoor residual spraying [IRS],

[1] A biochemical mode of action describes the manner in which pesticides interfere with the biochemistry of animals and plants.

[2] Entomological effect refers to a product's effect on a disease vector in terms of killing, inhibiting feeding, deterring, and reducing fertility or susceptibility to infection. Products with different biochemical modes of action may have similar entomological effects on target insects; for example, indoor residual spraying (IRS) formulations with pyrethroids and carbamates differ in their biochemical modes of action, yet are considered to have a similar impact on the target insect in areas of insecticide susceptibility.

[3] Formerly referred to as WHOPES Phase I evaluation

[4] Formerly referred to as WHOPES Phase II evaluation

[5] Formerly referred to as WHOPES Phase III evaluation

larviciding, etc.) should be consulted and updated to include details on the determination of non-inferiority.[6]

- Demonstrate non-inferiority to a first-in-class product in the product class, or another suitable comparator as identified by WHO, by means of entomological field trials (e.g., experimental hut trial studies in the case of ITN and IRS products).
- For pyrethroid-PBO nets, define a set of criteria for the bioavailability of PBO on the net over time, including not only that PBO is retained in the net, but also that it is replenished on the surface of the fibre after washing or during use.

The MPAC-endorsed recommendations specifically requested that WHO conduct further in-depth work on the assessment of non-inferiority of products within a class. While the ERG convened in 2017 acknowledged that entomological field studies – in particular experimental hut trials – are likely to provide a suitable approach for determining non-inferiority for some vector control interventions such as ITN and IRS products, it was recommended that the design of such trials be reviewed and additional guidance developed to support the implementation of standardized, rigorous study design and analysis. To support this process, an in-depth assessment of existing experimental trial data from different settings, along with a well-defined statistical methodology for analysing new and existing experimental trial data, was recommended. Specific guidance on the determination of non-inferiority should then be developed and incorporated into current WHO testing guidance.

WHO therefore convened an ERG on 5–6 July 2018 in Geneva, Switzerland to address these needs and to develop a methodology for determining the non-inferiority of candidate second-in-class products belonging to the ITN and IRS intervention types, with specific consideration given to an appropriate methodology for assessing the non-inferiority of pyrethroid-PBO nets.

OBJECTIVES OF THE ERG

The main objective of the ERG meeting was to develop a methodology for determining the non-inferiority of candidate second-in-class[7] ITN and IRS products. For ITNs, the methodology needed to be suitable for assessing pyrethroid-PBO nets, as this is an area of priority, but ideally it should also be applicable for comparing other ITN products within their respective product classes.

SPECIFIC ACTIVITIES OF THE ERG

The identified activities for the ERG were as follows:

1. Review existing data on laboratory and experimental hut studies conducted on pyrethroid